In Vivo Determination of the Complex Elastic Moduli of Cetacean Head Tissue

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Award Number: N00014-08-1-1158

LONG-TERM GOALS

The overall goal of this project is to develop and demonstrate a system for non-invasive *in vivo* measurement of the complex elastic moduli (stiffnesses and loss factors) of cetacean head tissues. This system is ultimately intended to provide a portable diagnostic capability for use in stranded animal assessments.

OBJECTIVES

The primary technical objective is to remotely generate and detect mid-frequency elastic waves within the body of a living cetacean and to use the measured propagation parameters of these waves to obtain the complex elastic moduli by inversion. A further technical objective is to extract tissue moduli in this manner intracranially. This objective carries considerably more technical risk since both the wave-generating ultrasound and the probe ultrasound will be attenuated, distorted and scattered by the passage through the skull. The final objective is to develop a prototype portable version of the technology and use it to perform examinations of stranded animals. Data collected with this system is envisioned to serve two purposes: 1) provide basic knowledge of in-vivo elastic properties, which is non-existent for marine mammals, and 2) provide a potential basis for non-invasive diagnostics of tissue pathologies, both naturally occurring or otherwise induced.

APPROACH

The foundation of the work is the capability to remotely generate elastic waves in soft tissues and observe their propagation with an ultrasound-based non-invasive system. The general approach for generation, reception and interpretation of the tissue wave fields is based on a new medical imaging technology called radiation force elastography[i]. These techniques, which have been demonstrated to some extent on human soft tissues, cannot be directly translated to use on cetacean head tissues due to the need to propagate through much thicker tissues and through skull bone, all the while keeping within safety limitations for ultrasound exposure[ii]. The current focus of the *in-vivo* program is to overcome these challenges through novel redesign of the concepts for both elastic wave generation and observation.

Report Documentation Page

Report Documentation Page	Form Approved OMB No. 0704-0188

1. REPORT DATE **2010**	2. REPORT TYPE	3. DATES COVERED **00-00-2010 to 00-00-2010**
4. TITLE AND SUBTITLE **In Vivo Determination of the Complex Elastic Moduli of Cetacean Head Tissue**		5a. CONTRACT NUMBER
		5b. GRANT NUMBER
		5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S)		5d. PROJECT NUMBER
		5e. TASK NUMBER
		5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) **Georgia Institute of Technology,G. W. Woodruff School of Mechanical Engineering,Atlanta,GA,30332**		8. PERFORMING ORGANIZATION REPORT NUMBER
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)		10. SPONSOR/MONITOR'S ACRONYM(S)
		11. SPONSOR/MONITOR'S REPORT NUMBER(S)
12. DISTRIBUTION/AVAILABILITY STATEMENT **Approved for public release; distribution unlimited**		
13. SUPPLEMENTARY NOTES		
14. ABSTRACT		
15. SUBJECT TERMS		

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT **unclassified**	b. ABSTRACT **unclassified**	c. THIS PAGE **unclassified**	**Same as Report (SAR)**	**7**	

Two embodiments of the wave generation system, involving different methods of shaping the forcing field, are being investigated. The first method involves generation of a line-like force and measurement of the waves which diverge from it. This requires a receiver or force generator whose focal volume is moved mechanically. A second embodiment is being studied wherein a ring-shaped forcing volume is formed by the ultrasonic source. As the ring radius is changed (through a change in the ultrasonic carrier frequency, for example), a fixed receiver measures the change in phase of the waves converging to the center of the ring. This approach has several potential benefits, the sum of which are expected to directly translate to improvements in the robustness of modulus estimation and safety with respect to ultrasound exposure.

The particle displacements resulting from the remotely generated elastic waves can be detected remotely using a modified version of an ultrasonic Doppler vibration measurement system called NVMS developed at Georgia Tech[iii]. Algorithms are being developed to enable the magnitude and phase of vibration to be determined, as well as the range (tissue depth) along the ultrasonic beam at which the vibration is being measured. By measuring the amplitude and arrival time of the shear wave at two different points (or from waves arriving from two different drive locations, as with the ring force excitation) the propagation speed and loss can be determined.

Elastic waves will be both remotely and directly generated in tissue phantoms and measured both remotely and directly to validate the measurement technique. The elastic properties of tissue phantoms will be obtained from remotely generated and measured data and compared with directly measured and tabulated material values. The noninvasive technique will be repeated for tissue phantoms enclosed in a simulated or hydrated real cetacean skull, and with harvested tissue samples. In-vivo testing will be conducted on Navy dolphins. Ultrasound parameters (peak negative pressure, time averaged intensity) will be consistent with limits established as safe for humans, and ultrasound frequencies will be kept high enough to be far above the highest frequency that is audible to the animals.

WORK COMPLETED

1. System simulation and design Analytical models of elastic wave fields generated by shaped ultrasound fields were developed and exercised in order to assist in defining the design of a new radiation force transducer and a companion NVMS transducer. Design specifications were developed, the transducers were ordered from a custom production house, and calibrations began.

2. NVMS development Further refinements were made to the system for determining elastic displacement time histories as a function of position using data from a single ultrasonic measurement (i.e. a depth-discriminating ultrasonic vibrometer). These were in the form of hardware and signal processing improvements, with a net result of improving measurement signal to noise ratio.

3. Hemorrhage and edema detection study The use of the prototype elastography system to detect hemorrhage or edema was studied through both finite element modeling and laboratory testing. The baseline finite element models were validated, and work progressed towards assessment of fluid/viscoelastic solid inclusion detection.

4. In vivo ultrasound testing Ultrasonic measurements were collected at several sites on the head of a Beluga Whale. This data was sought in order to gain experience with living subjects, and to assess backscatter and attenuation properties relative to tissue phantoms and samples used to date.

RESULTS

1. System Simulation and Design   An analytical model was developed to predict the elastic wave fields generated by 3-D ultrasonic intensity distributions in tissue-like materials. The model was used to compare and refine candidate designs for the new radiation force (remote low frequency wave motion generation) transducer and the companion NVMS (tissue motion sensing) transducer. Results from the model were also used to assess the precision of shear wave speed estimation with the elastography system, robustness with respect to ultrasound beam distortion or shifting, and quantify system safety margins relative to established ultrasound exposure limits[iv].

The final transducer designs, arrived upon from extensive exercise of the above model, were sent out for production by a custom transducer manufacturer. The radiation force generation (RF) transducer was received and charaterization testing began. An example result is shown in Figure 1, comparing predicted and measured normalized ultrasonic pressures in the focal plane at 800 kHz. The measured data show the same spatial features as the prediction, but with slightly lower sidelobes and a slight spatial contraction, both of which would be beneficial to system operation. Of greatest significance in the measurement is the strong central null and the well defined ring lobe structure, all of which should enhance shear wave speed estimation accuracy.

Figure 2 shows the measured and predicted-3dB normalized intensity contours in the focal plane for frequencies of 800 and 900 kHz. The lobe patterns shift inward with increasing frequency, as expected. The mean radius of the lobe pattern is illustrated with the thin dashed circles.

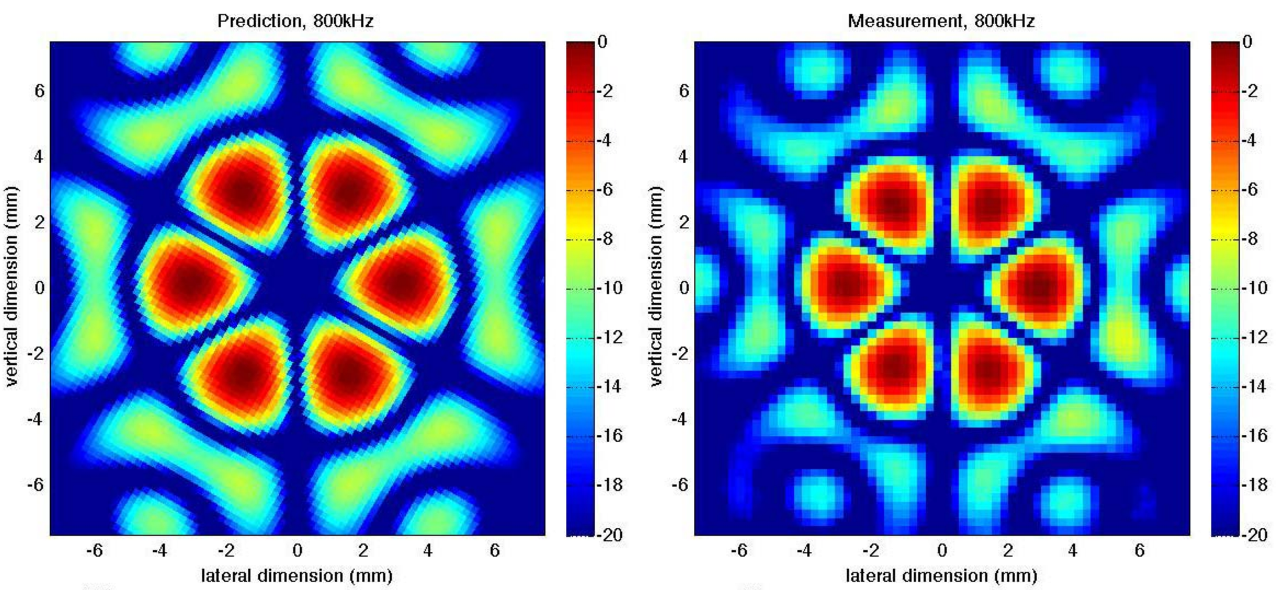

Figure 1. Predicted and measured normalized focal plane pressure distributions at 800 kHz, color levels in dB re maximum magnitude.

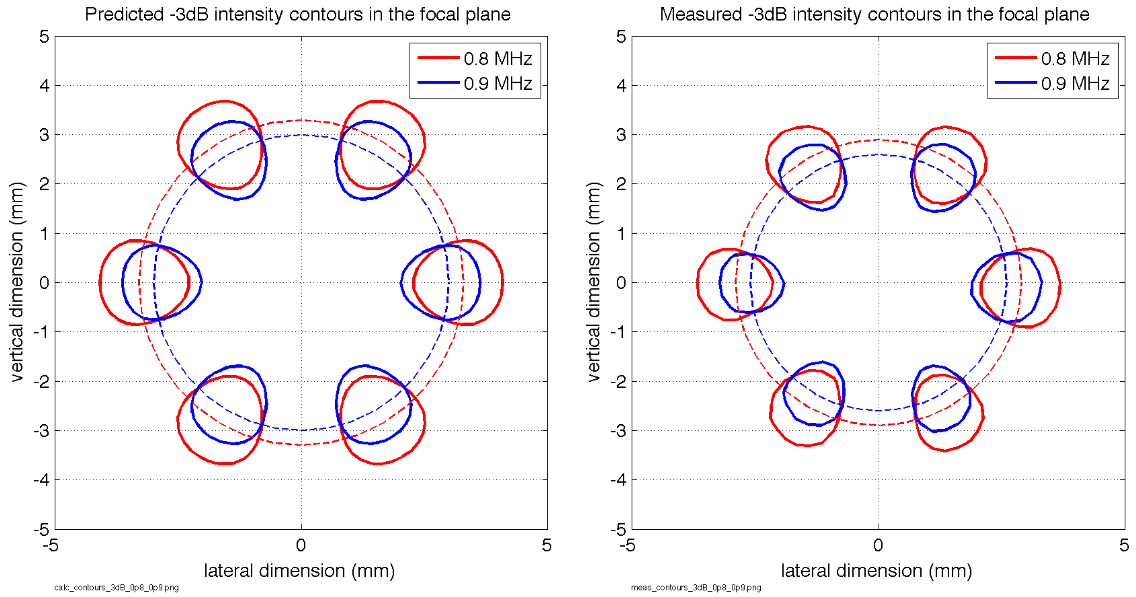

Figure 2. Predicted and measured -3dB intensity contours of the focal plane field at 800 and 900 kHz. The shift of the lobe pattern with increasing frequency is visualized with dashed circles.

The measured size of the change in mean radius is consistent with prediction. These results confirm the design concept that control of the ultrasonic carrier frequency provides control of the radius of the ultrasound-induced forcing field. This in turn provides the basis for measuring shear wave phase changes due to carefully controlled path length (mean radius) changes in order to extract shear speed.

2. NVMS development The primary hardware refinement to the NIVMS (tissue motion sensing system) was the replacement of the received signal's preamplifier with a LeCroy DA1855A RF differential amplifier. This offered two advantages over the fixed-gain preamplifier that was previously used, and allowed the system to take maximum advantage of the dynamic range available on its analog-to-digital (A-D) converter (a National Instruments PCI-5105). The first advantage was the preamplifier's variable gain, which allowed the signal level to be set to match the input range of the digitizer over a receive-level range of 40 dB. The second advantage was that the differential input of the amplifier allowed the signal that was directly transmitted between the two ultrasonic transducers (cross-talk) to be subtracted from the received signal prior to digitization. The net improvement resulting from these advantages was found to be a 9 dB increase in the measurement signal-to-noise ratio (SNR) when all other factors were held constant. The significance for system operation is the ability to detect displacements that are smaller by approximately a factor of three.

The signal processing for the vibrometer was improved in several ways. In the post-processing, spatial averaging was implemented to reduce measurement errors introduced by interference in the backscattered ultrasonic signal. Several algorithms were explored for doing this and a windowing function equivalent to the compression pulse envelope was found to offer the best compromise between spatial resolution and SNR. A variety of time-domain drive signals were also examined, and the study revealed the tradeoffs between incident energy and amplitude that limit vibrometer performance.

Interactions between the ultrasonic signals from the original radiation force generation source and the vibrometer were studied in detail. Modifications were made to both the vibrometer signal-processing algorithm and to the temporal and spectral characteristics of the sources driving signals in order to minimize these interactions and to permit the vibrometer to achieve optimal resolution in the presence of the potentially competing radiation-force signals. Although the ultrasonic vibrometer is inherently self-calibrating, as a part of this effort, the sensitivity of the vibrometer was independently verified by a series of comparison calibrations with neutrally buoyant accelerometers.

3. Hemorrhage and edema detection study The feasibility of detecting intracranial hemorrhage or edema was assessed through simulations and laboratory experiments. The general approach is to apply a translational mechanical vibration excitation similar to that employed in the practice of Magnetic Resonance Elastography in the human brain.[v] Vibration of the skull bone causes generation of shear waves in the brain tissue that can then be interrogated by the ultrasound vibrometer. The goal is to establish whether the presence and location of an inclusion can be inferred from these measurements.

Finite element models that simulated homogeneous brain tissue were made for validation of the FE solver when applied to a nearly-incompressible elastic solid with a low and complex shear modulus. A two dimensional plain-strain FE model was compared to a closed-form mathematical solution for a circular cylinder of infinite length and showed very close agreement. A three dimensional (3D) FE model was then developed for a finite length cylinder subjected to a translational motion normal to the length axis. A companion experiment was conducted using a tissue phantom inside a stiff layered cylinder, and using NVMS to observe resulting low frequency vibrations. General trends in the modeled and measured frequency response and shear-wave pattern were in agreement.

The validated homogeneous models were modified with inclusions of various properties and sizes. The material properties in a hematoma vary with time as the coagulation occurs beginning as a liquid, and transitioning to a soft elastic solid.[vi,vii] Therefore, the inclusion was modeled both as a liquid and as an elastic solid with material properties following Gennisson's data for porcine whole blood with a hematocrit of 50% (shear modulus of $490(1+0.02i)$ kPa and shear-wave speed of 0.68 m/s). Model results indicated that inclusions containing a viscoelastic material (e.g. clotting blood) could be readily detected using the proposed method. Results to date with inclusions containing inviscid liquids indicated that such volumes (e.g. edema) were more difficult to detect.

Development of tissue phantoms with inclusions of known properties began, with the goal of conducting experiments to compare with the above model results.

4. In vivo ultrasound testing Ultrasonic measurements were made on an adult male *Delphinapterus leucas* at the Georgia Aquarium under an approved animal use protocol. Testing was conducted in conjunction with a scheduled clinical examination. The NVMS transducer was used to collect backscatter data in the 1-3 MHz frequency range from tissues over and including the proximal mandibular bone and temporal fossa. The data were collected in order to assess parameters that influence overall elastography system performance, such as backscatter strength and variability as a function of ultrasound propagation depth, skin surface and bone scattering levels, and variation with anatomical position. Also of interest was how these values compared with the tissue phantoms in use for system testing in the laboratory. Generally, the phantoms had larger interfacial scattering and significantly lower attenuation. Although the testing was only conducted on a single animal, it proved highly valuable in terms of gaining experience with live subjects and field system development, all of which will aid in the development of the elastography field test system.

IMPACT/APPLICATIONS

There is considerable interest in the development of structural acoustic models for the cetacean head for two main reasons: 1) to better understand biomechanics of sound reception and production in cetaceans, and 2) to understand and hopefully mitigate any harmful effects of man-made sound on their health and behavior. The development and validity of these models is severely limited by an almost complete lack of knowledge of the mechanical properties of the constituent living tissue. There is thus considerable interest in being able to measure these properties *in vivo*. The techniques and instrumentation investigated here should also have biomedical diagnostic application, including non-invasive examinations of stranded animals.

RELATED PROJECTS

The NVMS vibrometer developed for the *in vivo* program was used to investigate the question of whether the pressure related (indirect) signal detected by the fish ear might be directional. It is generally believed that a fish localizes a sound source by detecting the acoustic particle acceleration vector via direct stimulation of the otolithic organs which function as triaxial accelerometers. Directional hearing experiments in cod, however, suggest that cod can determine the direction to a sound source at acoustic particle velocity levels which are subliminal. One possible explanation for this is that the pressure related signal, which is a result of the compliance of the swimbladder, might actually be directional due to the elasticity and elongation of the swimbladder. This concept was investigated theoretically using a finite element model and experimentally using the NVMS to measure the particle motion induced by a model swimbladder at the presumed location of the "sacculus" of a model fish. The swimbladder was an ovoid air cavity in a tissue phantom with the a small neutrally buoyant spherical reflector located at the measurement location. Directionality was observed in both the numerical and physical models, but only over a very restricted frequency range. The results were reported at the Second International Conference on the Effects of Noise on Aquatic Life, held in Cork, Ireland.

PUBLICATIONS

Martin, J.S., Rogers, P.H, and Gray, M.D., Range discrimination in multi-tone ultrasonic vibrometry: theory and experiment, submitted to the Journal of the Acoustical Society of America

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